Practical fundamentals of glass, rubber, and plastic sterile packaging systems

ARTICLE *in* PHARMACEUTICAL DEVELOPMENT AND TECHNOLOGY · FEBRUARY 2010

Impact Factor: 1.2 · DOI: 10.3109/10837450903511178 · Source: PubMed

4 AUTHORS, INCLUDING:

Gregory A Sacha
Baxter International Inc.
8 PUBLICATIONS **104** CITATIONS
SEE PROFILE

Wendy Clemmer
Baxter International Inc.
2 PUBLICATIONS **36** CITATIONS
SEE PROFILE

Karen Abram
Baxter International Inc.
1 PUBLICATION **28** CITATIONS
SEE PROFILE

Pharmaceutical Development and Technology, 2010; 15(1): 6–34

informa
healthcare

Practical fundamentals of glass, rubber, and plastic sterile packaging systems

Gregory A. Sacha , Wendy Saffell-Clemmer, Karen Abram, and Michael J. Akers

Research and Development, Baxter BioPharma Solutions, Bloomington, Indiana, USA

Abstract

Sterile product packaging systems consist of glass, rubber, and plastic materials that are in intimate contact with the formulation. These materials can significantly affect the stability of the formulation. The interaction between the packaging materials and the formulation can also affect the appropriate delivery of the product. Therefore, a parenteral formulation actually consists of the packaging system as well as the product that it contains. However, the majority of formulation development time only considers the product that is contained in the packaging system. Little time is spent studying the interaction of the packaging materials with the contents. Interaction between the packaging and the contents only becomes a concern when problems are encountered. For this reason, there are few scientific publications that describe the available packaging materials, their advantages and disadvantages, and their important product attributes. This article was created as a reference for product development and describes some of the packaging materials and systems that are available for parenteral products.

Keywords: *Sterile products; packaging; formulation development; glass; rubber; plastic*

Introduction and scope

Significant attention and effort are dedicated to the design of injectable formulations, development of analytical methods and manufacturing processes, and to the study of formulation stability. Frequently, much less attention is paid to the rational selection and study of sterile packaging systems. Scientists only direct their focus to the package when stability and compatibility problems occur that implicate the packaging system. Frankly, packaging development takes secondary priority to formulation, analytical and process development.

In searching the literature, there is a paucity of recent information regarding packaging development for sterile products. Therefore, this article was authored from the perspective of a fundamental tutorial of parenteral packaging that also attempts to incorporate much of the available recent literature. Articles are published when there are certain problems with packaging systems (e.g. extractables and leachables, latex sensitivity, glass delamination, particle problems, etc.), but there seems to be few, if any, extensive review articles focused on packaging development, especially for sterile dosage forms. Exceptions are book chapters on lyophilization containers and closures including specifics on glass and rubber.[1–3]

The Food and Drug Administration (FDA) published a guidance document that requires the evaluation of four attributes to establish suitability of materials and container-closure systems for pharmaceutical products.[4,5] These four attributes – protection, compatibility, safety, and performance/drug delivery – are featured throughout this article. There is specific focus on the chemical and physical properties, manufacturing, sterilization, product interactions and advantages and disadvantages of glass, rubber, and plastic materials used in sterile dosage form primary packaging. A brief discussion of packaging trends and advances involving more convenient drug delivery packaging systems is also included.

Address for Correspondence: Dr. Gregory A. Sacha, Research and Development, Baxter BioPharma Solutions, 927 S. Curry Pike, Bloomington, 47404, Indiana, USA. Email: gregory_sacha@baxter.com

(Received 16 July 2009; revised 25 November 2009; accepted 25 November 2009)

ISSN 1083-7450 print/ISSN 1097-9867 online © 2010 Informa UK Ltd
DOI: 10.3109/10837450903511178

Sterile product container systems

There are six basic primary packaging or container systems:

1. Ampoules – glass
2. Vials – glass and plastic
3. Pre-filled syringes – glass and plastic
4. Cartridges – glass
5. Bottles – glass and plastic
6. Bags – plastic

Generally, vials comprise about 50–55% of small volume injectable packaging, syringes 25–30%, with ampoules and cartridges filling the rest. Bottles and bags are the only packaging systems for large volume injectables. Usage of all packaging types, except ampoules, is increasing, especially pre-filled syringes. Each of these packaging systems for parenteral drug delivery has significant advantages and disadvantages. Generally, advantages involve user convenience, marketing strategy, handling during production and distribution, volume considerations, and compatibility with the product. The primary disadvantage with all these packaging systems is the potential reactivity between the drug product components and the packaging components. The reactivity is typically manifested through the appearance of particulate matter, detection of extractables, evidence of protein aggregation, and other physical and chemical incompatibilities.

Selection of the packaging system not only depends on compatibility with the product formulation and the convenience to the consumer, but also on the integrity of the container/closure interface to assure maintenance of sterility throughout the shelf-life of the product. Container/closure integrity testing has received significant attention and usually is an integral part of the regulatory submission and subsequent regulatory GMP inspections. It is beyond the scope of this manuscript to discuss the various container/closure integrity testing methods. However, it must be emphasized that formulation scientists developing the final product including the final package must appreciate the need to develop appropriate methods to assure proper seal integrity to protect the product during its shelf-life from any ingress of microbiological contamination. This testing is historically conducted using microbiological test methods. However, the FDA recognizes that microbiological test methods have scientific and practical limitations and encourages the development of methods that may be based on leak rate measurement if they are more useful for the particular application.[6,7]

Ampoules (Figure 1)

For decades, glass sealed ampoules were the most popular primary packaging system for small volume injectable products. Ampoules were favorable because they offer only one type of material (glass) to worry about for potential interactions with the drug product compared to other packaging systems that contain both glass or plastic and rubber.

Two disadvantages of glass ampoules are the assurance of the integrity of the seal when the glass tip is closed by flame and the problem of glass particles entering the solution when the ampoule is broken to remove the drug product. There exist 'easy-opening ampoules', weakened at the neck by scoring or applying a ceramic paint around the neck of the ampoule.[8] The paint weakens the glass at the point of application and permits the user to break off the tip at the neck constriction without the use of a file.[9] Nevertheless, glass particles will still enter the ampoule and this requires the use of a filter to withdraw product from the container. This disadvantage makes them a less common packaging option. Glass sealed ampoules still exist, but they are not the choice for new products in the United States. Elsewhere in the world, ampoule products are still widely used and still a popular package of choice for new sterile product solutions.

Glass ampoules are Type I tubing glass (Type I and tubing glass are discussed in more detail later.) in sizes ranging from 1–50 mL. After solution is filled into the top opening of the ampoule, the glass is heat sealed by one of two techniques – tip sealing or pull sealing. Tip sealing has the open flame directed toward the top of the ampoule that melts and seals itself while the ampoule is rotating on the sealing machine. Pull sealing has the open flame directed at the middle portion of the ampoule above the neck where the glass is melted while rotating and the top portion is physically removed during rotation. Thus the tip-sealed ampoule has a longer section above the neck while the pull-sealed ampoule has a more blunt, 'fatter' top.

Modifications of ampoules are available, e.g. wide-mouth ampoules with flat or rounded bottoms to facilitate filling with dry materials or suspensions.

Vials

The most common packaging for liquid and freeze-dried injectables is the glass vial (Figure 2). Plastic vials have made some ingress as marketed packages for cancer drugs, but may require more time before being commonplace in the injectable market. Plastic vials are made of cyclic olefin copolymer (COC). The appearance of a plastic vial looks identical to a glass vial (Figure 3).

Figure 1. Glass sealed ampoules (courtesy of Alcan Global Pharmaceutical Packaging, Inc.).

Figure 2. Different types of vials (courtesy of Alcan Global Pharmaceutical Packaging, Inc.).

Figure 3. Plastic vials (courtesy of Daikyo/West).

Reasons why plastic vials have not become as commonplace as glass vials include:

1. Challenges in introducing pre-sterilized containers into a classified (ISO 5) aseptic environment. Glass vials are sterilized and depyrogenated in dry heat tunnels that convey the vials directly into the aseptic environment without the need for manual transfer. Plastic vials are pre-sterilized (typically irradiation) at the vial manufacturer and the finished product manufacturer needs to determine how to aseptically transfer plastic vials into the aseptic environment. This is not easily accomplished, especially compared to the convenient way glass vials are introduced via the dry heat tunnels.
2. Challenges in handling and movement of much lighter weight containers compared to glass along conveyer systems on high-speed filling lines, with smaller vials (1–5 mL) especially difficult to process.
3. Concerns about potential interactions with the drug product (absorption, adsorption, migration, leachables) especially over a 2–3 year shelf life.

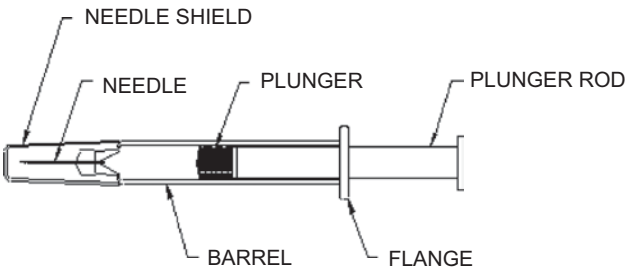
Syringes

Syringes are very popular delivery systems (Figure 4).[10–14] They are used either as empty sterile container systems where solutions are withdrawn from vials into the empty syringe prior to injection or as pre-filled syringes. Pre-filled syringes as a form of primary packaging are the focus of this section. Glass pre-filled syringes can be pre-sterilized by the empty syringe manufacturer or can be cleaned and sterilized by the finished product manufacturer. Plastic syringes can be purchased or some companies have the technology to apply form-fill-finish technologies for their own use.[15]

One company now has the capability to form-fill-finish glass syringes from tubing glass.[16] Other options regarding syringe size, components, formats, treatment of rubber materials, and manufacturing methods are summarized in Table 1. Most of the world's vaccines are packaged and delivered in syringes. The growth rate for products filled and packaged in pre-filled syringes increases about 13% per year.[17] This growth is related to the top factors that influence a physician's choice of a drug delivery type, which include ease of use by patients, convenience, and comfort.[17]

Primary reasons for syringe popularity include:

- The emergence of biotechnology and the need to eliminate overfill (reduced waste) of expensive biomolecules compared to vials and other containers. Vaccines, antithrombotics, and various home health care products such as growth hormone and treatments for rheumatoid arthritis and multiple sclerosis are more conveniently administered using pre-filled syringes.
- Availability of enormous (millions) quantities of pre-sterilized ready-to-fill syringes such as BD Hypak® SCF and BunderGlas RTF.
- The advent of contract manufacturers specializing in syringe processing with lower costs and high speed filling equipment.



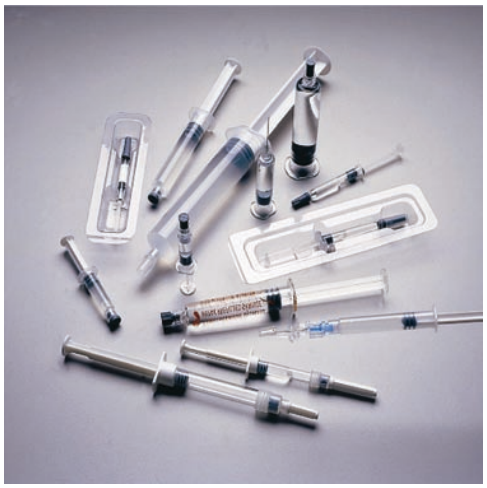


Figure 4. Syringe examples (courtesy of Baxter BioPharma Solutions).

Table 1. Pre-filled syringe options.

Sterilization	Pre-sterilized by empty syringe manufacturer and ready-to-fill, Supplied non-sterile, washed and sterilized by product manufacturer
Barrel size	0.5–100 mL; typically 0.5–10 mL
Needle format	Luer tip, use needle of choice, Staked needle affixed to syringe Hub, not used often
Needle gauge	21–32
Needle length	½ to ⅝ inch
Needle shield	Natural or synthetic rubber
Silicone application	Silicone oil or silicone emulsion, Applied at syringe manufacturer, Applied at finished product manufacturer
Silicone level	Varies, 0.6–1.0 mg per 1 mL syringe
Type of rubber plunger	Synthetic rubber (halobutyl)
Type of rubber septum (tip)	Natural or synthetic rubber, Plastic covers
Coating of rubber	Absent or use of fluoropolymer
Filling machine	Rotary piston peristaltic time-pressure, rolling diaphragm single head up to 10 heads, Up to 600 syringes filled per minute
Rubber plunger insertion	Insertion tube system, vacuum

- Elimination of dosage errors because, unlike vials, syringes contain the exact amount of deliverable dose needed.
- Ease of administration, because of elimination of several steps required before injection of a drug contained in a vial. Sterility assurance is increased, because fewer manipulations are required.
- More convenient for health care professionals and end users; easier for home use; easier in emergency situations.
- Reduction of medication errors and misidentification.
- Better use of controlled and potentially abusive drugs such as narcotics.
- Lower injection costs – less preparation, fewer materials, easy storage and disposal.

Syringe barrels can either be glass or plastic while syringe plunger rods are usually plastic. Plastic polymers for the syringe barrel include polypropylene, polyethylene, and polycarbonate. However, newer technologies are being developed in the area of 'glass-like' composite materials.

Syringes with needles may also have needle protectors (Figure 5) to avoid potential dangers of accidental needle sticks post-administration. Such protectors either can be part of the assembly or can be assembled during the finishing process. The use of these protection devices is increasing due to the 2000 United States Federal Needle Stick Safety and Prevention Act.[18] Needle stick prevention can be manual (shield activated manually by the user although there is still the risk of accidental sticking), active (automated needle shielding activated by user), or passive (automated needle shielding without action by the user).

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.